RESPIRATORY MEDICINE

CASE REPORT

Clinical equivalence between salbutamol hydrofluoroalkane pMDI and salbutamol Turbuhaler™ at the same cumulative microgram doses in paediatric patients

P. GUSTAFSSON*, S. KÄLLMAN* AND P. J. WHITEHEAD†

*Department of Paediatrics, Central Hospital, Skövde, Sweden, †GlaxoSmithKline Research and Development, Uxbridge, Middlesex, U.K.

Abstract This study aimed to demonstrate equivalent efficacy and safety between salbutamol delivered via the HFA134a pMDI (Hydrofluoroalkane 134a pressurised Metered Dose Inhaler) and the Turbuhaler™ dry powder inhaler in asthmatic children. This was a randomised, double-blind, double-dummy, placebo-controlled, crossover study in 10 asthmatic children aged 6–15 years who demonstrated at least 10% reversibility of FEV_1 after inhaling 400 μg of salbutamol. On 5 single study days subjects received either placebo or cumulative doses of 100, 200, 400 and 800 μg of salbutamol at 30 minute intervals. Both devices were placebo on one study day, while each device was active on two study days. FEV_1 was measured before and 20 minutes after each dose. Heart rate was measured before spirometry. Mean FEV_1 and heart rate at each time point and the area under the dose response time curve (AUC) were analysed using ANOVA. FEV_1 increased similarly after cumulative doses of salbutamol on each of the study days, irrespective of device. Mean treatment difference in AUC was 0.01L.min (95%CI –0.05 to 0.08L). Heart did not differ at any dose. It is concluded that salbutamol delivery from a HFA pMDI and Turbuhaler™ is equivalent on a microgram basis in asthmatic children for efficacy and safety.

Available online at http://www.sciencedirect.com

Keywords Metered-dose inhaler, Turbuhaler™, salbutamol, equivalence.

INTRODUCTION

The pressurised Metered-dose inhaler (pMDI) is the most commonly used metered-dose inhaler. Traditionally formulated with CFCs, it is now available with a new CFC-free propellant, hydrofluoroalkane 134a (HFA). Some patients (including the elderly and very young) can have difficulties in co-ordinating the use of pMDIs, but this can be largely overcome by using a spacer or using a breath-activated dry powder inhaler (DPI) instead (1).

Some DPIs (such as the Turbuhaler™ (TH)—Turbuhaler™ is a trademark of AstraZeneca Pharmaceuticals.) have been claimed to give better drug deposition in the lungs than the pMDI, resulting in higher efficacy (2,3). Data in adults have shown equivalent efficacy and safety between salbutamol delivered via the HFA pMDI or the TH (4), however, and the aim of the current study was to assess this in paediatrics.

Received 13 November 2001, accepted in revised form 20 March 2002
Correspondence should be addressed to: Dr P. Gustafsson, Department of Paediatric Clinical Physiology, Queen Silvia Children's Hospital, S-416 85 Göteborg, Sweden. Fax: +46 3184 1605; E-mail: pmgmed@artech.se

METHODS

Ten children aged 6–15 years (mean 12 years) with a history of asthma, ⩾10% reversibility from baseline in FEV_1 after inhaling 400 μg of salbutamol and demonstrated ability to use both devices, were enrolled into this randomised, double-blind, double-dummy, placebo-controlled, crossover study. Prior to enrolment the subjects' legal guardians gave written informed consent for their participation and the subjects gave their assent.

On 5 single study days, subjects received either placebo or cumulative doses of 100, 200, 400 and 800 μg of salbutamol at 30 min intervals. On each dosing occasion, they inhaled from both devices (according to the standard instructions supplied by the manufacturers) and received either an HFA pMDI (100 μg/actuation) and TH placebo, a TH (100 μg/actuation) and HFA pMDI placebo, or placebo from both devices. Both devices were placebo on 1 study day, while each device was active on 2 study days, the data from which were then combined for analysis to minimise variability. Dosing started at the same time on each study day (± 1 h) and the days were at least 46 h apart to avoid any carry-over effects. FEV_1 was measured using a turbine spirometer before and 20 min after each dose for three times on each occasion, and the highest value noted. The spirometer was checked daily using a 3 l precision syringe. Heart rate was measured before spirometry over 1 min using a stethoscope. Before dosing, subjects had to have withheld from taking short-acting β_2-agonists for 6 h and long-acting β_2-agonists for 12 h, and have a baseline FEV_1 within ±15% of their screening value.

The study was designed to show equivalence between the HFA pMDI and TH, defined as the 95% confidence intervals (95% CI) for the mean treatment difference being within ±0.25 l for FEV_1 and ±8 beats/min (bpm) for heart rate. Analysis of the mean FEV_1 and heart rate at each time point and the area under the dose response time curve (AUC) was performed using analysis of covariance, allowing for effects due to subjects, periods, predosing values and treatments.

RESULTS

FEV_1

FEV_1 increased similarly after cumulative doses of salbutamol on each of the study days, irrespective of delivery device (Fig. 1). The adjusted mean treatment difference between the HFA pMDI and TH was well within the equivalence criteria at each dose, e.g. after 100 μg it was 0.02 l (95% CI −0.05 to 0.09 l), and after 800 μg was 0.04 l (95% CI −0.05 to 0.12 l). The mean treatment difference in the AUC was 0.01 l.min (95% CI −0.05 to 0.08 l). Both devices were significantly better than placebo for both the increase in FEV_1 and the AUC ($P < 0.001$).

Heart rate

The adjusted mean treatment difference between the HFA pMDI and TH at each dose was well within the pre-defined equivalence limits. The largest difference (after 200 μg of salbutamol) was −2.4 bpm (95% CI −5.6 to 0.9), and at the maximum dose (800 μg) it was only −1.8 bpm (95% CI − 5.2 to 1.7). There was no difference in AUC observed between devices (mean treatment difference of −1.0 bpm min) [95% CI −3.0 to 1.1]), and no significant difference between either device and placebo.

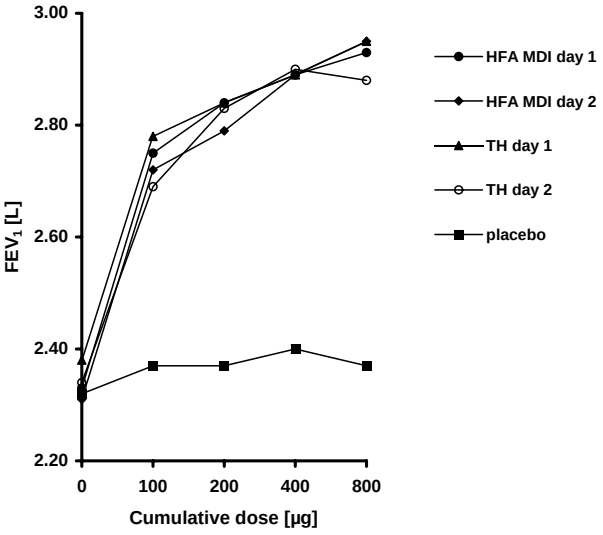

Fig. 1. Increase in FEV_1 after cumulative dosing.

DISCUSSION

This study demonstrates clinical equivalence between the pMDI and TH in children with asthma in terms of the effect of salbutamol on lung function (FEV_1) or the systemic parameter of heart rate. This is in accordance with adult data (4) and with other studies which have demonstrated equivalent efficacy between the TH and other DPIs such as the Diskus (5).

It has been claimed that only half the dose of drug is required from a TH when compared to either a pMDI or Diskhaler due to improved lung deposition (2,3,6,7). In these studies, the drugs were not compared at microgram equivalent doses, however, and they are contradicted by *in vitro* studies which show a more accurate dose of salbutamol and a higher fine particle mass from the pMDI than the TH (8). Furthermore, the effectiveness of a bronchodilator delivered from a TH is more dependent upon inspiratory flow than from a pMDI (9), except where inhalation from the pMDI is too fast. Taking all this together, therefore, we do not believe that there are any differences in the dose required to achieve similar relief between these two devices.

In conclusion, salbutamol delivery from a HFA pMDI and TH is equivalent on a microgram basis in children with asthma for both efficacy and safety.

Acknowledgements

This study was supported by GlaxoSmithKline Ltd. (study number SALL19).

REFERENCES

1. Pedersen S, Moretensen S. Use of different inhalation devices in children. *Lung* 1990; **168** (Suppl)**:** 653–657.
2. Thorsson L, Edsbäcker S, Conradsson TB. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered dose inhaler (pMDI). *Eur Respir J* 1994; **7:** 1839–1844.
3. Borgström L, Derom E, Ståhl E, Pauwels R. The inhalation device influences lung deposition of terbutaline inhaled via Turbuhaler or via a pressurized metered dose inhaler. *Am J Respir Crit Care Med* 1996; **153:** 1636–1640.
4. Méllen A, Arvidsson P, Palmqvist M, Lötvall J. Equivalent bronchodilation with salbutamol given via pMDI or Turbuhaler. *Am J Respir Crit Care Med* 1999; **159:** 1663–1665.
5. Arvidsson P, Méllen A, Palmqvist M, Lötvall J. Equivalent therapeutic ratio of salbutamol given by Turbuhaler® and Diskus™. *Respir Med* 2000; **94:** 574–577.
6. Löfdahl C-G, Andesson L, Bondesson E, *et al*. Differences in bronchodilating potency of salbutamol in Turbuhaler as compared with a pressurized metered-dose inhaler formulation in patients with reversible airway obstruction. *Eur Respir J* 1997; **10:** 2474–2478.
7. Carlsson L-G, Arweström E, Friberg K, Källén A, Lunde H, Löfdahl C-G. Efficacy of cumulative doses of salbutamol administered via Turbuhaler® or Diskhaler® in patients with reversible airway obstruction. *Allergy* 1998; **53:** 712–715.
8. Prime D, Grant AC, Slater AL, Woodhouse RN. A critical comparison of the dose delivery characteristics of four alternative inhalation devices delivering salbutamol: pressurised metered dose inhaler, *Diskus* inhaler, *Diskhaler* inhaler and *Turbuhaler* inhaler. *J Aerosol Med* 1999; **12:** 75–84.
9. Hirsch T, Peter-Kern M, Koch R, Leupold W. Influence of inspiratory capacity on bronchodilatation via Turbuhaler® or pressurized metered-dose inhaler in asthmatic children: a comparison. *Respir Med* 1997; **91:** 341–346.